ORAL DRUG DELIVERY SYSTEM

This application claims the benefit of U.S .Provisional Application No. 60/433,116, filed December 13, 2002, and of U.S. Provisional Application No. 60/517,464, filed November 4, 2003.

FIELD OF THE INVENTION

The invention relates to dosage forms comprising formulations of drugs. More specifically, this invention relates to formulations that include High Viscosity Liquid Carrier Materials (HVLCMs) and their use to deliver drugs.

BACKGROUND

Techniques and compositions for drug delivery of pharmaceuticals, including oral delivery, are well known. For example antihistamines, decongestants and antacids are all commonly delivered in solid tablet form. Analgesics have been delivered orally in tablet form for many years, for example salicylic acid, morphine, Demerol™ (meperidine), codeine and Percocet™ (oxycodone). Controlled release and sustained release pharmaceutical compositions have also been available for many years; for example the Contac 400 Time Capsule ™ (Phenylpropanolamine Hydrochloride and Chlorpheniramine Maleate), anti-psychotics, melatonin formulations provide release of an active agent over several hours. Analgesics are of particular interest for controlled release formulations, and common controlled release formulations for analgesics include the OxyContin® (oxycodone), MS Contin™ (morphine), CS Contin™ (codeine).

Formulation of drugs for delivery, particularly oral delivery, poses certain challenges. One challenge is to produce an oral controlled-release dosage form that provides for a relatively steady dose of drug over the approximately eight hours during which the dosage form passes through the gastrointestinal tract. Sustained release is often achieved by providing the tablet with a coating that delays release, or by formulating the tablet in such a way that it disintegrates relatively slowly, releasing drug as it does so. A tablet, however, once ingested, is subject to considerable mechanical and chemical stresses as it

passes through the esophagus, stomach, duodenum, jejunum, ileum, large intestine and colon, thus providing a significant challenge in maintaining controlled release of the drug formulation. Acids, enzymes and peristalsis can cause the tablet to break apart, resulting in exposure of the inside of the tablet and an increase in surface area of the tablet material. This will tend to increase the delivery rate of the drug or otherwise adversely affect the controlled release properties of the dosage form.

Another challenge, is to produce a dosage form, including an oral dosage form, that reduces the potential for drug abuse. In particular, opioids, CNS-depressants, and stimulants are commonly abused. According to a 1999 study by the National Institute on Drug Abuse (NIDA), an estimated 4 million people, about 2 percent of the population age 12 and older, were (at the time of the study) using prescription drugs "non-medically." Of these, 2.6 million misused pain relievers, 1.3 million misused sedatives and tranquilizers, and 0.9 million misused stimulants.

While many prescription drugs can be abused, the most common classes of abused drugs are: (1) Opioids - often prescribed to treat pain, (2) CNS Depressants - used to treat anxiety and sleep disorders, and (3) Stimulants - prescribed to treat narcolepsy and attention deficit/hyperactivity disorder.

Opioids are a class of potent narcotics that includes, for example, morphine, codeine, oxycodone and fentanyl and related drugs. Morphine is often used to alleviate severe pain. Codeine is used for milder pain. Other examples of opioids that can be prescribed to alleviate pain include oxycodone (e.g. OxyContin®-an oral, controlled release form of the drug); propoxyphene (e.g. Darvon™); hydrocodone (e.g. Vicodin™); hydromorphone (e.g. Dilaudid™); and meperidine (e.g. Demerol™).
In addition to relieving pain, opioids can also produce a sensation of euphoria, and when taken in large doses, can cause severe respiratory depression which can be fatal.

CNS depressants slow down normal brain function by increasing GABA activity, thereby producing a drowsy or calming effect. In higher doses, some CNS depressants can

become general anesthetics, and in very high doses may cause respiratory failure and death. CNS depressants are frequently abused, and often the abuse of CNS depressants occurs in conjunction with the abuse of another substance or drug, such as alcohol or cocaine. Many deaths occur yearly through such drug abuse. CNS depressants can be divided into two groups, based on their chemistry and pharmacology: (1) Barbiturates, such as mephobarbital (e.g. Mebaral™) and pentobarbital sodium (e.g. Nembutal™), which are used to treat anxiety, tension, and sleep disorders. (2) Benzodiazepines, such as diazepam (e.g. Valium™), chlordiazepoxide HCl (e.g. Librium™), and alprazolam (e.g. Xanax™), which can be prescribed to treat anxiety, acute stress reactions, and panic attacks. Benzodiazepines that have a more sedating effect, such as triazolam (e.g. Halcion™) and estazolam (e.g. ProSom™) can be prescribed for short-term treatment of sleep disorders.

Stimulants are a class of drugs that enhance brain activity - they cause an increase in alertness, attention, and energy that is accompanied by increases in blood pressure, heart rate, and respiration. Stimulants are frequently prescribed for treating narcolepsy, attention-deficit hyperactivity disorder (ADHD), and depression. Stimulants may also be used for short-term treatment of obesity, and for patients with asthma.

Stimulants such as dextroamphetamine (Dexedrine™) and methylphenidate (Ritalin™) have chemical structures that are similar to key brain neurotransmitters called monoamines, which include norepinephrine and dopamine. Stimulants increase the levels of these chemicals in the brain and body. This, in turn, increases blood pressure and heart rate, constricts blood vessels, increases blood glucose, and opens up the pathways of the respiratory system. In addition, the increase in dopamine is associated with a sense of euphoria that can accompany the use of these drugs.

Taking high doses of a stimulant can result in an irregular heartbeat, dangerously high body temperatures, and/or the potential for cardiovascular failure or lethal seizures. Taking high doses of some stimulants repeatedly over a short period of time can lead to hostility or feelings of paranoia in some individuals.

A common and particularly dangerous cocktail of drugs is produced when stimulants are mixed with antidepressants or over-the-counter cold medicines containing decongestants. Anti-depressants may enhance the effects of a stimulant, and stimulants in combination with decongestants may cause blood pressure to become dangerously high or lead to irregular heart rhythms, which in extreme cases may be fatal.

Solid dosage forms are particularly susceptible to abuse. For example, tablets oral drug delivery can be ground down into a powder. Drug addicts and abusers grind down the tablet in order to nasally inhale the drug. Addicts also grind the tablet to extract the drug into alcohol or water to make a concentrated injectable drug solution. Administration of various abused drugs in this way produces a sudden high dose of drug into the blood stream making the user euphoric. These well-known techniques for drug abuse have been used for many years with all manner of drugs.

One particularly important example of a highly addictive drug that is commonly abused by crushing (for nasal inhalation), and/or alcohol or water extraction (for intravenous injection) is Oxycodone. Oxycodone is a powerful analgesic that is available in tablet form (Oxycontin®, Purdue Pharmaceuticals) and is manufactured in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths. The Oxycontin® tablets are formulated as time-release tablets (about 12 hours of release), but of course crushing and grinding down the tablet destroys any controlled-release properties. It has been alleged that Oxycontin® abuse has so far resulted in at least 120 deaths nationwide (http://www. stopoxycontinaddiction.com/oxycontin-addiction.htm). 5mg of Oxycontin® has as much active ingredient (oxycodone) as one Percocet™. So chewing/snorting a crushed 40mg Oxycontin® is like taking eight Percocet™ at once or a 80mg Oxycontin® is like taking 16 Percocet™ all at once. Overdose produces small pupils, slow breathing, dizziness, weakness, seizures, the loss of consciousness, coma, and sometimes death.

The above problems present a clear and long-felt challenge to drug manufacturers to produce drug dosage forms that also allow for desirable drug release kinetics and reduced potential for abuse.

SUMMARY OF THE INVENTION

The invention relates to a dosage form comprising a formulation, the formulation comprising a drug, a HVLCM, a network former, and an optional rheology modifier. The formulation may also include a solvent. In another aspect, the invention relates to an oral dosage form comprising a formulation having a drug, wherein the formulation, upon exposure to an aqueous environment, forms a network within the formulation and an outer surface. The formulations of the invention show desirable drug-release kinetics and/or abuse deterrence characteristics.

The invention relates to a drug delivery device comprising a formulation, the formulation comprising a HVLCM, a network former and an optional rheology modifier, and, in certain embodiments also comprising a solvent. In another aspect, the invention relates to a drug delivery device comprising a formulation, wherein the formulation, upon exposure to an aqueous environment, forms a network within the formulation and an outer surface. These devices can be used to deliver any type of biologically active compound including drugs for example opioids, CNS depressants and stimulants. In a another embodiment, the invention relates to an oral dosage form comprising a formulation, the formulation comprising a HVLCM and an opioid. In a more specific embodiment, the formulation contains oxycodone, sucrose acetate isobutyrate (SAIB), cellulose acetate butyrate (CAB), isopropyl myristate (IPM) and ethyl lactate (EL).

A particular advantage of the dosage form and delivery device of the invention is that, in a particular embodiment, it provides an oral dosage form comprising a formulation having a drug, comprising one or more of an HVLCM, a network former, a rheology modifier, and a solvent, present in amounts effective to reduce the rate of extraction of the drug, for example, with water, ethanol, or other solvents, while simultaneously providing desired drug release kinetics. This reduced rate of extraction contributes to abuse deterrence and reducing risk of diversion.

BRIEF DESCRIPTION OF THE FIGURES

FIGS 1-4, and 11 are graphs that show representative results from an abuse-deterrence study. The units of the graphs are relative percentage cumulative release vs. time (minutes).

FIG. 5 is a graph from a representative dog pharmacokinetic (PK) study showing plasma concentration (ng/ml) vs. time (hr) for three SAIB soft gelcaps containing oxycodone formulations (A, B and C); compared with an Oxycontin® tablet.

FIG. 6 is a chemical schematic showing the structure of SAIB, which is a hydrophobic, fully esterified sucrose derivative, at a nominal ratio of six isobutyrates to two acetates.

FIG. 7 is a graph showing representative dissolution results of drug in a simulated gastrointestinal environment (cumulative % release vs. time).

FIG. 8 is a representative photograph of a 100% SAIB formulation following exposure to temperature at –80 °C (-112 °F) for eight hours and crushing with a hammer. Note the controlled release matrix structure is preserved.

FIG. 9 is a representative photograph of a formulation comprising SAIB + solvent, following exposure to temperature at –80 °C for eight hours and crushing with a hammer.

FIG. 10 is a representative photograph of a formulation of the invention (PTI-821, which is SAIB:EL:IPM:CAB at a ratio of 67:26:3:4) contained in a soft gelatin capsule, and containing 9 mg of drug) formulation following exposure to temperature at –80 °Cfor eight hours and crushing with a hammer.

SPECIFIC EMBODIMENTS OF THE INVENTION

Abbreviations used throughout the disclosure are as follows:

HVLCM: High Viscosity Liquid Carrier Material

SAIB: Sucrose Acetate Isobutyrate

EL: Ethyl Lactate

IM (or IPM): Isopropyl Myristate

CAB: Cellulose Acetate Butyrate

OC (or OXY): Oxycodone free base or salt

A derivative of a compound refers to any molecule the structure of which is based on the structure of the original compound. The derivative may have substituted substituent groups or may have additional groups added, or may have groups removed, but it substantially shares the same core structure as the original compound. Derivatives of compounds include for example the free bases, salt, and the hydrates of such compounds.

Drug delivery device refers to a device for holding or containing and releasing a drug wherein after administration of the drug delivery device to a subject, in particular, a human subject, the drug is released from the drug delivery device into a subject. The device for holding or containment may be any type of containment device, including injectable devices (pumps etc) and ingestible devices, including a tablet, pill, capsule or formulation. Many drug delivery devices are described in *Encyclopedia of Controlled Drug Delivery* (1999), Edith Mathiowitz (Ed.), John Wiley & Sons, Inc.

Drug refers to any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of any disease, disorder, or condition or intended to affect the structure or function of the body, other than food. It can include any beneficial agent or substance that is biologically active or meant to alter animal physiology

Dosage form refers to a drug and a drug delivery device.

Formulation refers to one or more ingredients or compounds. For example, a drug formulation is any drug combined together with any pharmaceutically acceptable excipients, additives, solvents, carriers and other materials.

High Viscosity Liquid Carrier Materials (HVLCMs) refers to non-polymeric, non-water soluble liquids with a viscosity of at least 5,000 cP at 37 °C that do not crystallize neatunder ambient or physiological conditions. HVLCMs may be carbohydrate-based, and may include one or more cyclic carbohydrates chemically combined with one or more carboxylic acids, such as Sucrose Acetate Isobutyrate (SAIB). HVLCMs also include nonpolymeric esters or mixed esters of one or more carboxylic acids, having a viscosity of at least 5,000 cP at 37 °C, that do not crystallize neat under ambient or physiological conditions, wherein when the ester contains an alcohol moiety (e.g., glycerol). The ester may, for example comprise from about 2 to about 20 hydroxy acid moieties. Various HVLCMs used with the present drug-delivery system are described in U.S. Patent Nos. 5,747,058; 5,968,542; and 6,413,536, all incorporated by reference hereby. The present invention may employ any HVLCM described in these patents but is not limited to any specifically described compounds.

Rheology modifier refers to a substance that possesses both a hydrophobic and a hydrophilic moiety. Rheology modifiers used with the invention generally have a logarithm of octanol-water partition coefficient of between about –7 and +15, preferably between –5 and +10, more preferable between –1 and +7. Rheology refers to the property of deformation and/or flow of a liquid, and rheology modifiers are used to modify viscosity and flow of a liquid formulation. Rheology modifiers include, for example, caprylic/capric triglyceride(Migliol 810), isopropyl myristate (IM or IPM), ethyl oleate, triethyl citrate, dimethyl phthalate, and benzyl benzoate.

Network former refers to a compound that forms a network structure when introduced into a liquid medium (such as a HVLCM). Network formers may be added to the liquid formulation (such as a HVLCM) such that, upon exposure to an aqueous environment, they form a three dimensional network within the formulation. Network formers include,

e.g., cellulose acetate butyrate, carbohydrate polymers, organic acids of carbohydrate polymers and other polymers, hydrogels, as well as particles such as silicon dioxide, ion exchange resins, and/or fiberglass, that are capable of associating, aligning or congealing to form three dimensional networks in an aqueous environment.

Solvents refers to any substances that dissolve another substance (solute). Solvents may be used in an HVCLM formulation to dissolve other components such as drugs, network formers, rheology modifiers and stabilizers. Solvents may include alcohols, organic acids and their derivatives, esters of organic acids, and compounds possessing an alcohol and an organic acid residue e.g., ethyl lactate (EL) or triacacetine, dimethyl sulfoxide (DMSO), propylene carbonate, N-methylpyrrolidone (NMP), ethyl alcohol, benzyl alcohol, glycofurol.

Stabilizer refers to any substance used to inhibit or reduce degradation (e.g., chemical) of other substances with which the stabilizer is mixed. Exemplary stabilizers typically are antioxidants that prevent oxidative damage and degradation, e.g., sodium citrate, ascoryl plamitate, vitamin A, and propyl gallate and/or reducing agents.

In situ refers to laboratory conditions simulating conditions in the GI tract of a mammal (see table 1).

Placebo refers to formulations without active drug (e.g., "a placebo solution" in Table 1).

Detailed Description

Please note that the examples described herein are illustrative only and in no way limit the scope of the invention.

Dosage forms and drug-delivery devices suitable for delivery of a drug are disclosed. Certain of these devices are suitable for the oral delivery of a drug. The dosage form or device includes a formulation that includes an HVLCM and one or more of a network

former, an optional rheology modifier and/or a solvent. In particular, the formulation can be loaded with a drug, and will release the drug over a period of time when in an aqueous environment, and in particular, an environment similar to that of the GI tract of a mammal. While not wishing to be bound by theory, it is believed that the network former allows the formation of a micro-network within the formulation upon exposure to an aqueous environment. This micro-network formation appears to be due, at least in part, to a phase inversion (e.g., a change in glass transition temperature, T_g) of the network former. The result is believed to be a skin or surface layer of precipitated network former at the interface between the dosage form and the aqueous environment of the GI tract, as well as the formation of a three-dimensional micro-network of precipitated network former within the dosage form.

Preferred dosage forms comprising drug delivery devices of the invention do not become substantially emulsified during passage through the GI tract, but substantially maintain their integrity (deformability and/or surface characteristics), while passing through the GI tract and releasing drug. While not wishing to be bound by any theory, it is believed that the formulation forms a network on the surfaces and/or in the bulk phase. The surfaces are renewed, such that the concentration gradient is maintained at the surfaces for desirable drug release kinetics. This phenomenon was observed by the inventors during the dog plasma PK study that produced the results as shown in Fig. 5. The dosage form when exiting the GI tract may retain a substantial proportion of its weight; for example, desirable dosage forms can have a weight that is no less than about 50% of the weight of the dosage form upon oral administration. This percentage weight may vary with different formulations used in dosage forms, and may be at least 60%, 70%, 80%, or even 90% of the original weight.

In preferred embodiments, the formulation comprises a HVLCM along with various additives and excipients. HVLCMs used in certain embodiments are generally hydrophobic, non-polymeric, non-water soluble liquids with a viscosity of at least 5,000 cP at 37 °C that do not crystallize neat under ambient or physiological conditions. Various HVLCMs used with the invention are described in U.S. Patent Nos. 5,747,058;

5,968,542; and 6,413,536 and in U.S. Serial Nos. 09/699,002, filed October 26, 2000 and 10/316,441, filed December 10, 2002, the entire contents of which are incorporated herein by reference. Sucrose Acetate Isobutyrate (SAIB) has been found to be a particularly suitable HVLCM for many of the applications described herein.

The dosage forms and drug delivery devices of the invention can be used to deliver any type of biologically active compound. Examples of such biologically active compounds delivered using the invention include opioids, CNS depressants and stimulants, as well as proteins, hormones, chemotherapeutic agents, anti-nausea medication, antibiotics, antivirals and other agents. One class of drug of particular interest for delivery using the system disclosed herein is opioids, which includes alfentanil, allylprodine, alphaprodine, anileridine, apomorphine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, cyclorphen, cyprenorphine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxyaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydroxymethylmorphinan, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, methylmorphine, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, ohmefentanyl, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, pholcodine, piminodine, piritramide, propheptazine, promedol, profadol, properidine, propiram, propoxyphene, remifentanyl, sufentanyl, tramadol, tilidine, naltrexone, naloxone, nalmefene, methylnaltrexone, naloxone methiodide, nalorphine, naloxonazine, nalide, nalmexone, nalbuphine, nalorphine dinicotinate, naltrindole (NTI), naltrindole isothiocyanate, (NTII), naltriben (NTB), nor-binaltorphimine (nor-BNI), beta-funaltrexamine (b-FNA), BNTX, cyprodime, ICI-174,864, LY117413, MR2266, etorphine, DAMGO, CTOP, diprenorphine, naloxone benzoylhydrazone, bremazocine, ethylketocyclazocine, U50,488, U69,593, spiradoline, DPDPE, [D-Ala2,Glu4] deltorphin, DSLET, Met-

enkephalin, Leu-enkephalin, ß-endorphin, dynorphin A, dynorphin B, a-neoendorphin, or an opioid having the same pentacyclic nucleus as nalmefene, naltrexone, buprenorphine, levorphanol, meptazinol, pentazocine, dezocine, or their pharmacologically effective esters or salts.

The dosage form disclosed allows for the release of drug including over a prolonged period, such as of several hours. The total period for release of drug in an amount sufficient to be an effective dosage may be greater than 20 hours, or greater than 17 hours, or greater than 15 hours, or greater than 12 hours, or greater than 10 hours, or greater than 8 hours, or greater than 6 hours, or greater than 4 hours, or greater than 2 hours, or greater than 1 hour. The amount of drug sufficient to provide an effective dosage is determined from the therapeutic range of the drug, which is determined from, for example, clinical trials, and this information is easily available to one of skill in the art.

The drug delivery device disclosed may include various components in addition to the carrier material (generally a HVLCM). The additional compounds may be present in amounts ranging from about 75 wt% to as low as about 0.01 wt% of the total formulation. These additional components may include the following types of compounds:

- Solvents, e.g., ethyl lactate (EL) or triacetine, DMSO, Propylene carbonate, NMP, Ethyl alcohol, Benzyl alcohol, Glycofurol, alpha-tocoperol, Miglyol 810, isopropyl alcohol, diethyl phthalate, PEG 400, triethyl citrate, benzyl benzoate.
- Network formers, e.g., cellulose acetate butyrate (CAB 171-15, CAB 381-2 and CAB 381-20, supplied by Eastman Chemicals, the characteristics of which are described in Table 2); carbohydrate polymers, organic acids of carbohydrate polymers and other polymers, hydrogels, as well as particles such as silicon dioxide, ion exchange resins, and/or fiberglass, that are capable of associating, aligning or congealing to form three dimensional networks in an aqueous environment. Other examples include cellulose acetate phthalate, ethyl cellulose, Pluronic, Eudragit, Carbomer, hydroxyl propyl methyl

cellulose, cellulose acetates such as CA 381-2 and cellulose triacetate, PMMA, CAB 500-5.

•Rheology modifiers, e.g., caprylic/capric triglyceride(Migliol 810), isopropyl myristate (IM or IPM), ethyl oleate, triethyl citrate, dimethyl phthalate, and benzyl benzoate.

•Stabilizers, e.g., antioxidants such as sodium citrate ascorbyl palmitate, and propyl gallate and/or reducing agents. Other examples include ascorbic acid, vitamin E, sodium bisulfite, butylhydroxyl toluene, BHA, acetylcysteine, monothioglycerol, phenyl –alpha-nathylamine, lecithin, EDTA.

These and other additional compounds (discussed in greater detail below) may be altered so as to control the rate of release of a drug and/or the maximum dosing (e.g. solubility) of a drug used with the drug delivery device of the invention (Handbook of Pharmaceutical Excipients 3rd ed., A. Kibbe, Am. Pharm. Assn., pub.).

In certain embodiments, the orally-administered, drug delivery device disclosed may be formulated so as to produce particular controlled plasma levels of drug over a particular period. This is obviously of great importance in maintaining a drug-plasma level within an appropriate therapeutic range. An appropriate therapeutic range will vary depending on the drug, but can range from femtogram/ml levels up to above microgram/ml levels for a desired period of time. For example, a single dose of a drug dosage form disclosed herein may result in maintenance of plasma levels of a drug at greater than 5 ng/ml for a period of greater than 8 hours (See Fig. 5, discussed in detail below). In other embodiments, the drug plasma level achieved using a single dose may be greater than 5 ng/ml for a period of greater than 10 hours, greater than 12 hours, greater than 14 hours, greater than 16 hours, greater than 18 hours, or greater than 20 hours. In yet other embodiments, the drug plasma level achieved using a single dose may be greater than 5 ng/ml, greater than 10 ng/ml, greater than 15 ng/ml, greater than 20 ng/ml, greater than 30 ng/ml, greater than 40 ng/ml, greater than 50 ng/ml for a period of 4, 8, 10, 12, 14, 16, 18 or 20 hours.

The maximum plasma concentration of drug may be reached at a time following administration from between 0.1 hr to about 24 hr, or from about 0.25 hr to 10 hr, or from

about 0.25 hr to 8 hr, or from about 0.5 hr to 6 hr, or from about 0.5 hr to 4 hr, or from about 0.5 hr to 2 hr, or from about 0.5 hr to 1 hr. The time to maximum plasma concentration may be adjusted by adjusting various components of the drug delivery device as taught herein. Altering components alters viscosity or other rheological characteristics of the formulation and concomitantly alters rate of drug release (discussed in detail below). The rate of reduction of plasma drug concentration over time may also be adjusted by varying components of the drug delivery device. Any desired release profile may be achieved by altering components as described herein.

The plasma levels obtained may be adjusted by adjusting the formulation and other components of the drug delivery device, and desirable plasma levels will depend on the therapeutic range or its index for any particular drug. It is readily within the skill of one in the art to determine the desired therapeutic index, and in view of the current disclosure, it would be a matter of routine experimentation to adjust the various components in order to achieve the desired release characteristics for a particular drug.

In certain embodiments, the release profile of drug over the release period is preferably approximately steady over time, sufficient to provide a therapeutic dose over the release period, and preferably shows a decreased burst effect when compared to a standard tablet formulation. As can be seen from Fig. 7 (discussed in more detail later), the drug delivery device of the invention can release drug (in this case, oxycodone) at an approximately steady rate over a period of at least 24 hours. The release rate is particularly steady from about 1 hr to greater than 24 hrs. This is in contrast to a commercial tablet formulation (OxyContin®) that provides substantial drug release during the first 5 hr period. In the case as shown in Fig. 7, the dosage form using the drug delivery device of the invention provides a long term in vitro release with less than 40% of drug released within 24 hours, whereas the commercial dosage form provides nearly 100% release in 24 hours. The time to 90% release of drug may be varied by varying the formulation and other device components and may be as little as 4 hours, 6 hours, 8 hours, 10, hours,12 hours, 16 hours or 20 hours, or up to about 24 hours.

The rate of drug release from the dosage form may be varied depending on the drug used and dosage required. Release rates may be different in different parts of the GI tract, and release rates may be averaged over the time of transit through the GI tract (approximately 8 – 24 hrs). Typical average release rates may vary substantially. For many drugs, they may range from about 0.01 to 500 mg/hr, from 0.5 to 250 mg/hr, 0.75 to 100 mg/hr, 1.0 to 100 mg/hr, 2.0 to 100 mg/hr, 5 to 100 mg/hr, 10 to 100 mg/hr, 10 to 80 mg/hr, 20 to 50 mg/hr, or about 20 to 40 mg/hr.

Dosage regimens for the drug may be determined by the physician in accordance with standard practices. Once per day or twice per day (BID) dosing may be used to maintain a sufficient clinical effect, e.g., to maintain pain relief.

An important advantage of the dosage forms disclosed herein is that they have abuse-deterrent characteristics and/or reduced risk of diversion. The dosage form, and the formulation contained therein is not susceptible to crushing, powdering or extraction using ethanol or water. Specifically, HVLCM is a viscous liquid, and so formulations containing HVLCMs avoid the possibility of crushing for the purpose of inhalation. Additionally, the formulation of the invention has the characteristic of being resistant to drug extraction using ethanol or water, when compared to a tablet formulation of a drug.

In certain preferred embodiments, the drug-delivery device is composed of a drug formulation encapsulated within an enclosure or capsule, preferably biodegradable, such as a capsule or a gelatin capsule ("gelcap"), wherein the capsule is made of a substance that degrades or otherwise dissociates when exposed to conditions present in the gastro-intestinal tract of a mammal. Capsules and gelcaps are well known in drug delivery technology and one of skill could select such a capsule as appropriate for delivery of a particular drug. Once the capsule has dissolved or dissociated from the formulation, the formulation of the invention generally remains intact, especially for hydrophobic formulations, and passes through the GI tract without emulsification or fragmentation.

In certain more specific embodiments the invention encompasses an oral dosage form comprising a formulation contained within a biodegradable capsule, wherein the formulation comprises a drug and a HVLCM, and wherein the capsule is made of a substance that degrades when exposed to conditions present in the gastro-intestinal tract of a mammal. In certain embodiments the capsule comprises gelatin or synthetic polymers such as hydroxyl ethyl cellulose and hydroxyl propylmethyl cellulose. Gelcaps can be of the hard or soft variety. Gelatin capsules are well suited for delivering liquid formulations such as vitamin E and cod-liver oil. Gelatin capsules are stable in storage, but once in the acid environment of the stomach (low pH less than about pH 4-5), the gelcap dissolves over a 10-15 minute period. In certain embodiments, the drug delivery device further comprises at least one component selected from the group consisting of: Ethyl Lactate, Triacetin, Propylene Carbonate, Glycofurol, Triethyl Oleate, Isopropyl Myristate, Cellulose Acetate Butyrate, and derivatives thereof.

Certain preferred embodiments of the orally-administered, drug-delivery device of the invention comprise Sucrose Acetate Isobutyrate (SAIB) as the HVLCM carrier material. SAIB is a non-polymeric highly viscous liquid at temperatures ranging from –80 °Cto over 100C, it is a fully esterified sucrose derivative, at a nominal ratio of six isobutyrates to two acetates (Figure 6). It is manufactured by Eastman Chemical Company as a mixed ester, and the resulting mixture does not crystallize but exists as a very viscous liquid. It is a hydrophobic, non-crystalline, low molecular weight molecule that is water insoluble and has a viscosity that varies with temperature. For example, pure SAIB exhibits the viscosity of approximately 2 million centipoise (cP) at room temperature and approximately 600 cP at 80C. SAIB has unique solution-viscosity relationship in that the SAIB solutions in a number of organic solvents is significantly lower than these viscosity values for the pure SAIB and therefore the SAIB-organic solvent solutions render themselves capable of processing using conventional equipment such as mixers, liquid pumps and gelcap production machines. SAIB also has applications in drug formulation and delivery, for example as described in US Patent Nos. 5,747,058, 5,968,542, 6,413,536, 6,498,153, all incorporated by reference herein. In the present invention, SAIB may be used as the HVLCM and may be present in quantities that vary

significantly. For example, quantities of at least about 50, 60, 70, 80, 90, 95, 97, 98, 99, 99.5 or 99.9 wt% can be used. Various formulations containing SAIB are discussed in the examples.

In addition, certain embodiments of the drug delivery device as disclosed allow the oral delivery of compounds, such as proteins, that would not normally be considered effectively orally administrable because administration in conventional oral compositions would likely result in the breakdown of the active agent by stomach acids or enzymes.

One embodiment of the invention relates to opioid dosage forms suitable for oral administration, including those that provide desirable drug release kinetics and/or limit the likelihood that diversion of the opioids in the dosage forms could occur by patients or others. In this embodiment, the opioids can be dissolved or dispersed in the formulation component of the invention, which can be simply a HVLCM. Suitable opioid compounds deliverable according to the invention include, for example, those generally used as pain relievers, narcotics and/or anesthetics, and include alfentanil, allylprodine, alphaprodine, anileridine, apomorphine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, cyclorphen, cyprenorphine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxyaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydroxymethylmorphinan, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, methylmorphine, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, ohmefentanyl, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, pholcodine, piminodine, piritramide, propheptazine, promedol, profadol, properidine, propiram, propoxyphene, remifentanyl, sufentanyl, tramadol, tilidine, naltrexone, naloxone, nalmefene, methylnaltrexone, naloxone methiodide, nalorphine, naloxonazine, nalide, nalmexone, nalbuphine,

nalorphine dinicotinate, naltrindole (NTI), naltrindole isothiocyanate, (NTII), naltriben (NTB), nor-binaltorphimine (nor-BNI), beta-funaltrexamine (b-FNA), BNTX, cyprodime, ICI-174,864, LY117413, MR2266, etorphine, DAMGO, CTOP, diprenorphine, naloxone benzoylhydrazone, bremazocine, ethylketocyclazocine, U50,488, U69,593, spiradoline, DPDPE, [D-Ala2,Glu4] deltorphin, DSLET, Met-enkephalin, Leu-enkephalin, ß-endorphin, dynorphin A, dynorphin B, a-neoendorphin, or an opioid having the same pentacyclic nucleus as nalmefene, naltrexone, buprenorphine, levorphanol, meptazinol, pentazocine, dezocine, or their pharmacologically effective esters or salts.

The oral dosage forms of these opioids may be prepared by simply mixing a HVLCM, a rheology modifier, a network former, the active agent, a solvent and any additives, and introducing the resulting mixture into a gelatin capsule. Alternative formulations may include emulsifying the mixture in water, and introducing this emulsion into the gelatin capsule, or using one or more of the techniques described herein to produce the dosage form.

In another embodiment of the invention, the HVLCM can be used as the continuous phase in a dispersion of particulate biologically active agent. For example, SAIB, which is extremely viscous, can be used to suspend particles of lyophilized protein, microparticles, microspheres, or microcapsules of drugs, for example, biologically active agents, to produce suspension formulations. Concentrations of the active agent in the suspension formulation are analogous to those disclosed above. The resulting suspension formulation has excellent storage stability.

Preferred embodiments of this invention provide an effective, user-friendly and inexpensive ingestible oral dosage form that allows sustained drug release, with favourable drug-release kinetics, during transit through the gastro-intestinal tract, and is less subject to abuse than current tablet and capsule dosage forms. The invention encompasses a controlled release oral drug delivery device. One drug delivery device of

this invention encompasses a SAIB-drug formulation which may be enclosed in a gelatin capsule suitable for oral delivery. Different embodiments may use some or all of the following additional components in the formulation to effect appropriate drug delivery kinetics: Solvents, e.g., ethyl lactate (EL) or triacacetine, DMSO, Propylene carbonate, NMP, Ethyl alcohol, Benzyl alcohol, Glycofurol. Network formers, e.g., cellulose acetate butyrate (CAB 171-15, CAB 381-2 and CAB 381-20 supplied by Eastman Chemicals). Rheology modifiers, e.g., caprylic/capric triglyceride(Migliol 810) and other plasticizers such as isopropyl myristate (IM or IPM), triethyl citrate, dimethyl phthalate, and ethyl oleate, benzyl benzoate. Stabilizers, e.g., antioxidants such as sodium citrate ascoryl plamitate, and propyl gallate. A specific example of a formulation for use in the drug delivery device of the invention contains oxycodone free base and/or hydrochloride salt, SAIB, ethyl lactate, isopropyl myristate, and CAB. An exemplary embodiment, used by the inventors to produce data disclosed herein, is formulated as follows: oxycodone free base 10mg per gelcap, SAIB 65%, ethyl lactate 27%, isopropyl myristate 3% and CAB 381-20 5% (all percentages are weight percent). This formulation is placed into a soft gelcap.

The dosage form of the invention may comprise one or more drugs. The amount of drug(s) and percentages of components in the formulation may vary. Typical average amounts may vary substantially. For many drugs, they may range from about 0.1 mg to 1000 mg, or from about 1 mg to 500 mg, or from about 2mg to 250 mg, or from about 2mg to 250 mg, or from about 2mg to 150 mg, or from about 5mg to 100mg, or from about 5mg to 50 mg. The precise amount of drug desired can be determined by routine methods well known to pharmacological arts, and will depend on the type of drug, and the pharmacokinetics and pharmacodynamics of that drug.

The percent weight of HVLCMs may vary depending on the characteristics of the dosage form desired, and may be for example include from about 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, 99.5%, to about 100%. Exemplary formulations disclosed herein contain 99%, 71%, 70%, 65%, 63%, 61.6%, 59%, 50%, 40%, 30%, 20% or even lesser amounts of SAIB. Variation in SAIB content may be made to alter viscosity or other

rheological properties of the formulation and to alter the rate at which drug is delivered. Using the information presented here, ones skilled in the art could alter the SAIB content of the formulation to suit various drugs of differing hydrophobicity or hydrophilicity, and determine the optimum rate of drug release from the formulation.

The dosage form of the invention may comprise one or more solvents. The percent weight of solvent(s) (such as EL) may vary depending on the characteristics of the dosage form desired, and may be for example from about 0% to about 60%, or from about 20% to about 50%, or from about 25% to about 48%. Exemplary formulations disclosed herein include those with 48%, 45%, 36.3%, 31.4%, 29.5%, 29%, 27%, and 23% EL. Again, using the information presented herein, ones skilled in the art could adjust the percent of solvent and determine the optimum amount required for delivery of a particular drug. More than one solvent can be used in a SAIB formulation.

The dosage form of the invention may comprise one or more rheology modifiers. The percent weight of rheology modifier(s) may vary depending on the characteristics of the dosage form desired, and may be for example vary from about 0.1% to about 10%, or from about 0.5% to about 5%, or from about 1% to about 4%. Exemplary formulations disclosed herein include those with 3.5%, 3%, and 1%, and 0%, IM. Using the information presented herein, ones skilled in the art could adjust the percent of formulation viscosity or other rheology modifier and determine the optimum amount required for delivery of a particular drug. More than one rheology modifier can be used in a SAIB formulation.

The percent weight of network former(s) may vary depending on the characteristics of the dosage form desired, and may be for example from about 0% to about 20%, or from about 0.1% to about 10%, or from about 0.5% to about 9%, or from about 1% to about 8.6%. Exemplary formulations disclosed herein include those with 8.6%, 7.8%, 5%, 4.5%, 3%, 2.1%, 2%, 1%, 0.5% and 0% CAB. Different types of CAB (e.g., CAB 381-20, CAB 381-2, and CAB 171-15) may be used to affect desired drug release characteristics. Again, using the information presented herein, ones skilled in the art

could adjust the percent of the network former and determine the optimum amount required for delivery of a particular drug. More than one network former can be used in a SAIB formulation.

The formulations of the invention may use network formers such as cellulose acetate butyrate of varying acetyl and butyryl content such as CAB 381-20, CAB 381-2 and CAB 171-15. CAB allows the in-situ formation of a micro-network within the SAIB-drug formulation. Although not wishing to be bound by theory, it appears that the mechanism of micro-network formation appears in part to be due to phase inversion (e.g., change in T_g) of network formers. That is to say, when SAIB formulations containing the CAB type of network former (for example CAB 381-20) are exposed to or immersed in aqueous environments such as the mammalian gastrointestinal (GI) tract, previously dissolved network formers in SAIB formulations will precipitate as a result of migration of water and other biologically available fluid components, which will result in polymer precipitation process and yield polymeric networks within the drug delivery device. The formation of micro-network will begin at the surface of the formulation mass and the polymeric network will gradually propagate toward the center of the formulation mass, resulting in a progressive increase in SAIB formulation viscosity in situ.

In conjunction with the network formers, solvents such as ethyl lactate, and rheology modifiers such as isopropyl myristate, when formulated into SAIB, appear to confer a number of unexpected characteristics to the HVLCM formulations. The characteristics include rheological (e.g., viscosity) characteristics, drug release kinetics, and abuse-deterrence characteristics.

It was discovered that the drug release rates in the early and/or late time periods increased with increasing content of the network forming polymers in the presence of varying concentration of ethyl lactate and isopropyl myristate. However, the effects of ethyl lactate (EL) varied, and, for example, during early time periods (0-6 hours) increasing EL concentration increased the drug release rate while in late time periods (from 6-24 hours), the drug release rate decreased with increasing concentration of EL. Also, notably, drug

extractability from SAIB drug formulations using ethanol solutions consistently decreased with addition of CAB polymers regardless of the concentrations of ethyl lactate and isopropyl myristate.

Also, it was discovered that addition of CAB polymer in SAIB formulations consistently raised the viscosity of the SAIB formulations before and after immersion in 37 °C aqueous media. However, the addition of other components i.e., ethyl lactate and isopropyl myristate was discovered to decrease viscosity before water immersion, but increase viscosity following the immersion in water. These observations are highly unexpected based on a previous understanding of solvents and plasticizers in SAIB drug formulations.

The present invention allows for adjustment of a number of performance characteristics of HVLCM formulations by adjusting the ratios of individual formulation ingredients such as solvents, rheology modifiers and network formers, including optimization thereof. The current invention also discloses new and surprising interrelationships between the formulation ingredients, which resulted in unique and non-obvious formulation rheology, drug release kinetics, rate and extent of drug absorption in vivo, and/or desirable abuse deterrence characteristics including reduced drug extractability, for example, by alcoholic or aqueous solutions.

The invention provides a dosage form that reduces or eliminates drug abuse wherein the route of abuse may include, for example snortable, inhalable, intravenous, sublingual, bucal, subcutaneous, percutaneous, vaginal, rectal or intraocular means. The present dosage form has several important abuse-deterrent characteristics: it is non-crushable (for abusive nasal inhalation) and it provides a formulation, e.g., that makes alcohol-extraction or water-extraction of the drug very difficult, producing a poor drug yield.

The dosage forms of the invention show unexpectedly favourable drug-release kinetics. For example, the SAIB/Oxycodone formulation provides improved pharmacokinetic parameters such as shorter Tmax, greater and/or equivalent Cmax and AUC (area under

curve) and improved bioavailability of the drug when compared with a currently marketed formulation (e.g., OxyContin®).

Another unexpectedly favourable property of the formulation of the invention is that the formulation bolus appears to stay substantially intact as it passes through the GI tract. For example, the SAIB-based formulation is released from the gelatin capsule when the capsule is dissolved, but the formulation bolus itself is not emulsified as it passes through the stomach, gut or colon despite being, it is believed, kneaded or deformed by GI motility (peristaltic motion). While not wishing to be bound by theory, it is believed that surface renewal occurs by relatively constant renewal of surface drug concentration by diffusion of the drug from the interior of the bolus, and by deformation and refolding of the surface, or by some combination of these mechanisms.

In a particular embodiment, the invention provides an oral dosage form comprising a formulation contained within a biodegradable capsule, wherein the formulation comprises a drug, a HVLCM, a rheology modifier, a network former and a solvent, and wherein the capsule is made of a substance that degrades when exposed to conditions present in the gastro-intestinal tract of a mammal. In preferred embodiments, the HVLCM can be SAIB, and the capsule can be made from gelatin or synthetic polymers. In particular embodiments the drug may be an opioid such as oxycodone. The drug-release kinetics of dosage forms incorporating various formulations can be seen to be both unexpected and favorable for delivery of drugs such as oxycodone.

Preparation of Formulations

A method for preparation of an exemplary formulation of the invention, using SAIB as the HVLCM, is presented. Other SAIB formulations can be prepared by varying this method. The ratios refer to weight percent ratios for SAIB/Ethyl lactate/Isopropyl Myristate/CAB 381-20, respectively.

A formulation comprising SAIB/EL/IPM/CAB (65:27:3:5) was made as follows:

An appropriate amount ethyl lactate was placed in a beaker; while stirring slowly CAB and IPM were added (stir bar on stir plate); allowed to go completely into solution (stir bar on stir plate)- resulting mixture was left at 37 °C for 3 days; hot (80 °C) SAIB (shake in hand, then place on stir plate) was added - 65:27:3:5 mixture left over a period of about 48 hrs at 37 °C; the mixture was heated to 70 °C for ~2 hours and homogenized with 20mm probe at about 4000 rpm for 20-30 seconds; oxycodone-base was added (at 9mg/g) and the mixture heated to 70 °C for 1 hr, then left overnight. The mixture was reheated to 70 °C to fill soft gelcaps using a hypodermic needle and matching syringe.

Formulations, Viscosity and Dissolution (Table 1)

Table 1 displays viscosity and dissolution data for various formulations. Viscosity values were determined at 26 °C and 37°C (+/- 0.1 to 0.3°C) using Brookfield Digital Rheometer Models LV DV III and HBDV and CPE 52 cone (n=1 ea). The content of oxycodone ranged from 9 to 12 mg per gelcap in SAIB formulations (lot#X03502 contains only SAIB and oxycodone).

In addition to the compositions of SAIB formulations, Table 1 also shows viscosity at 37 °C for the formulations, both before and after immersion in 37 °C water for 6 hours (the column marked "placebo – H_20" refers to the viscosity of the solution before immersion in water, and the column marked "placebo + H_20" refers to the viscosity of the solution following immersion in water). The conditions of 37 °C and water immersion were intended to simulate in vivo conditions.

Table 1 also shows cumulative amount of oxycodone released (mg) during two separate periods. One period is for 0 to 6 hours, and the other for 6 to 24 hours.

Information in Table 1 was analyzed and the following semi-empirical equations were derived (see equations 1-3). Equations 1-3 were derived from the information in Table 1 for SAIB oxycodone gelcap formulations X03511 to X03518 (8 different formulations).

Equation 1 demonstrates that the drug dissolution rate from time intervals 0-6 hours increases with the increasing concentrations of EL, IPM and CAB polymers (statistical confidence is high, r = 0.9).

Equation 2 shows that the drug dissolution rate from 6-24 hours increases with increasing IPM and CAB but decreases with increasing EL.

Equation 3 shows that the drug dissolution rate from 0 to 24 hours increases with the increasing EL, IPM and CAB.

The results embodied in the equations 1-3 are unexpected. One would have expected that increased CAB would decrease the dissolution rate. Instead increasing CAB appears to increase dissolution rate in the presence of EL and IPM. In addition, the role of EL changes depending on the time intervals of interest.

Equations 4-5 were calculated using formulation viscosity values before immersion in 37 °C water for 6 hours. As can be seen in equations 4-5, the correlation coefficient is excellent (r2=0.93 to 0.96). Both equations predict that viscosity will increase with increasing CAB while the viscosity will decrease with increasing EL and IPM. Based on the theories of solution rheology, this was expected.

Equations 6-7 were derived from the formulation viscosity values following immersion in water at 37 °C for 5 hours. As can be seen in these equations, as expected, increasing CAB increases viscosity following immersion in water. However, equation 6 and 7 both predict that increasing EL increases the immersion viscosity. This is unexpected. One would expect that the effect of increasing EL on immersion viscosity would be to decrease viscosity.

Table 1 displays data for the SAIB-oxycodone formulation X03502. X03502 did not contain any formulation ingredients (pure SAIB), but it did deliver a significant amount of oxycodone during the dissolution testing (0.42 mg over 0-6 hours and 0.65mg over 6-

24 hours). As can be seen by the in situ viscosity data (51,200cP), which is significantly reduced in situ, it released oxycodone at a low rate but with a good rate control mechanism.

Table 1 also shows a number of other interesting formulations. For example X03503 (SAIB/IPM 99/1), which shows a significant rheology modification effect of 1% IPM, showed higher drug delivery rate compared with pure SAIB formulation.

In addition, table 1 presents SAIB formulations containing CAB 171-15. As can be seen in formulations X03505 to X03508 viscosity before and after immersion in water are quite significantly different from those formulations containing CAB 381-20BP. As a result SAIB oxycodone formulations containing CAB 171-15 exhibited significantly different release kinetics of oxycodone from those containing equivalent weight percent of CAB 381-20.

Below are the semi-empirical equations that were deduced from the dissolution experiment data. The equations can be used to calculate Oxycodone free base dissolution and extraction, and viscosity of placebo SAIB solutions before and after immersion in 37 °C Water for 5 hours.

<u>1. Dissolution of Drug With Varying Wt% of Components</u>

Cumulative drug dissolution was measured as functions of weight percent of EL, IPM and CAB 381-20BP. Eight SAIB-Oxycodone formulations with corresponding in vitro dissolution data are shown. Formulations were used in non GLP and GLP dog PK studies. Lots X03511 to X03518 (n = 8).

For the following equations Y = cumulative amounts of drug dissolved (mg) or extracted (wt.%), and x1, x2 and x3 are the weight percents of EL, IPM and CAB 381-20BP, respectively.

a. Time interval from 0 to 6 hrs.

$$\frac{1}{Y1} = 3.02 - 0.15\sqrt{x1} - 0.5\sqrt{x2} - 0.37\sqrt{x3} \ : r^2 = 0.9 \qquad \text{(equation 1)}$$

b. Time interval from 6-24 hrs.

$$\frac{1}{Y2} = 1.59 + 0.054\sqrt{x1} - 0.355\sqrt{x2} - 0.41\sqrt{x3} \ : r^2 = 0.95 \qquad \text{(equation 2)}$$

c. Time interval from 0-24 hrs.

$$\frac{1}{Y3} = 1.05 - 0.002\sqrt{x1} - 0.21(\sqrt{x2} + \sqrt{x3}) \ : r^2 = 0.93 \qquad \text{(equation 3)}$$

<u>2. Viscosity of SAIB Placebo Solutions at 37 °C, before and after Immersion in Water.</u>

(a) For SAIB Placebo Solutions Containing CAB 381-20BP (n =13) Before Immersion in Water at 37 °C:

$$Z = 3359.02 - 192.26\,x1 - 227.88\,x2 + 1240.29\,x3 : : r^2 = 0.93 \qquad \text{(equation 4)}$$

Alternative Correlation

$$\text{Ln } Z = 8.47 - 0.1x1 - 0.137x2 + 0.585x3 : : r^2 = 0.96 \qquad \text{(equation 5)}$$

(b) For SAIB Placebo Solutions Containing CAB 381-20BP(n=13) After Immersion in Water @37 °C for 5 hours:

$$\text{Ln } Z1 = 3.8 + 0.056x1 - 0.00911x2 + 1.02x3 : : r^2 = 0.96 \qquad \text{(equation 6)}$$

Alternative Correlation is

$$Z1 = -\ 42327.04 + 292.95x1 + 405.64\,x2 + 12173.84x3 : : r^2 = 0.8 \ \text{(equation 7)}$$

Where Z and Z1 are the viscosity (cP) of SAIB placebo solutions before and after immersion in 37 °C water for 5 hours.

The above equations and equation 8, given below, derived with respect to an exemplary drug (oxycodone) allow one to formulate dosage forms in which the abuse deterrence and drug release kinetics, as well as other characteristics, can be varied and optimized to any

desired extent. Similar equations can be developed with respect to other exemplary drugs.

Table 1: Rheological Characteristics and In Vitro Drug Release Attributes of SAIB Oxycodone Formulations

Lot #	Composition (wt %)	Viscosity (cP) at 37°C		Dissolution Attributes (mg of drug released over 0-6 and 6-24 hr)	
		Placebo -H20	Placebo +H20	Σ 0-6 hr (mg)	Σ 6-24 hr (mg)
X03502	SAIB (100)	137,000	51,200	0.42	0.65
X03503	SAIB/IPM (99/1)	79,773	33,338	0.63	0.78
X03504	SAIB/EL/CAB 171-20 (50/48/2)				
X03505	SAIB/EL/CAB 171-15 (50/45/5)	2,046	1.14x10E(6)	2.82	3.53
X03506	SAIB/EL/CAB 171-15 (70/27/3)	1,618-2,670	5,270-9,380	1.09/1.45	2.33/2.27
X03507	SAIB/EL/CAB 170-15 (61.6/36.3/2.1)	325	-		
X03508	SAIB/EL/CAB 171-15 (70/29.5/0.5)	48	262	1.21	2.76
X03511	SAIB/EL/IMP/CAB 381-20 BP (59/31.4/1/8.6)	6,296	120e3	1.7	3.1
X03512	SAIB/EL/IMP/CAB 381-20BP (59.8/31.4/1/7.8)	35,720	346,000	1.42	2.4
X03513	SAIB/EL/IPM/CAB 381-20 BP (71/23/1/5)	3,274	4,092	1.02	1.74
X03514	SAIB/EL/IPM/CAB 381-20BP (65/27/3.5/4.5)	2,892	14,349	1.61	2.83
X03515	SAIB/EL/IPM/CAB 381-20BP (65/27/3/5)	4,040-7,010	31,221-30,427	1.7	2.74
X03516	SAIB/EL/IPM/CAB 381-20BP (63/29/3/5)	2,920	38,000	2.11	3.1
X03517	SAIB/EL/IPM/CAB 381-20BP (63/29/3.5/4.5)	875	5,300	1.97	2.84
X03518	SAIB/EL/IPM/CAB 381-20BP (65/27/3/5)	4,040-7,010	31,221-30,427	2	3.1
X03520	SAIB/EL/CAB 171-15 (70/27/3)	1,618-2,670	5,270-9,380	1.64	2.5

Table 2: Exemplary CABs

CAB types (supplied by Eastman Chemicals	Butyryl Content (%)	Acetyl Content (%)	Hydroxyl Content (%)	Melting Point (°C)	Glass Tran. Temp (°C)	Molecular Wt (no. avg)
171-15	17	29.5	1.5	127-240	NA	NA
381-2	36-38	13.5-14.5	1.3-1.7	171-185	130-133	40000
381-20	36	15.5	0.8	185-196	128	66000-83000

Measurement of Drug Dissolution Rates in Low pH Solution (FIG. 7)

One soft gelcap containing one of several SAIB-oxycodone formulations was placed in a standard glass beaker with a stirrer mechanism (as defined by United States Pharmacopia Apparatus II; VK 7000 USP II Dissolution Tester). 900 ml of 0.1N HCL solution at 37 °C was placed in the beaker and the solution was stirred at 50 rpm for 2 hours. During this period, the gelcap dissolved and the SAIB drug formulation was exposed to the low pH solution, and oxycodone dissolution begins. A number of 1ml samples were taken and oxycodone concentration determined by HPLC (Perkin Elmer Series 200 LC Pump, or equivalent; UV detector, Perkin Elmer Diode Array Detector 235C, or equivalent). Following the initial dissolution step, the content of the beaker was modified to adjust pH from 1 to 6.8 by adding sodium phosphate buffer. Temperature was maintained at 37 °C, and dissolution of drug continued for additional 22 hours. Additional samples of 1 ml were taken at various time points and oxycodone concentration determined by HPLC. The cumulative percentage of oxycodone dissolved into the media was calculated for each time interval and a graph drawn (FIG. 7).

Figures 7 show the data obtained from a drug dissolution experiment. The graph shows the data for a SAIB-drug formulation in a soft gelcap (square data points) compared with a commercial oxycodone tablet (OxyContin®) (diamond data points) that was used as a reference. The y-axis represents cumulative percent of oxycodone released and the x-axis represents time (hrs).

The SAIB oxycodone formulation of Fig. 7 contained the following weight percents of ingredients: oxycodone free base 10mg per gelcap, SAIB 65%, ethyl lactate 27%, isopropyl myristate 3% and CAB 381-20 5%. The commercial oxycodone product contained 80 mg of oxycodone. A number of other SAIB oxycodone gelcap formulations were tested for drug dissolution and results are given in Table 1.

It is apparent from Figure 7 that the commercial oxycodone tablet showed a large initial burst of oxycodone release with nearly 50% being delivered within the first hour, and

80% delivered within six hours. The drug release following the burst was slow as compared with the initial burst. On the other hand, the SAIB oxycodone formulation showed no burst effect and displayed a more controlled and sustained release of the drug over the entire testing period.

Extraction of Drug Into Ethanol

An important feature of the invention is that formulations can be made such that extraction of drug from the formulations using traditional ethanol extraction (traditionally used by drug abusers) is much less efficient than it is for the tablet and capsule formulations of the prior art.

FIGS 1-4 and 11 are graphs that show results from an abuse-deterrence study. The aim was to determine the amount of oxycodone that could be extracted from a dosage form comprising a SAIB/oxycodone formulation in a soft gelcap using simple alcohol extraction, as used by drug abusers. The units of the graphs are percentage cumulative release vs. time (mins).

The method used to produce data for the abuse-deterrence study was as follows. Each soft gelcap was filled with 0.75 ml of formulation and was placed in 18 ml of 0.1N HCL in a 60-mL amber bottle and shaken at 240 RPM on an orbital shaker for 30 minutes. After 30 minutes, 12 ml of 200° (200 proof) ethanol was added to each bottle. The solutions were swirled by hand and a 1-ml sample was sampled from each bottle at T=0. The solutions were placed back in the orbital shaker for further shaking at 240 RPM. 1 ml samples were taken after 10, 20, 30, 40, 60 and 180 minutes of further shaking from each bottle. The results were graphed on a linear scale of cumulative release (%) vs. Time (mins).

FIG. 1 shows percentage cumulative amounts of drug extracted in percentage of initial drug loading in SAIB formulations vs. time (mins) for 9 formulations. Each formulation contains 12 mg/ml oxycodone. The formulation ID numbers and formulations

component ratios are shown in the key. The ratios (weight percent) of each ingredient correspond to: SAIB:EL:IM:CAB.

From the data presented in Figure 1, it can be seen that all ingredients and their ratios affect the extractability of drug. Using a regression analysis, the following empirical equation relating cumulative percent of drug extracted as a function of weight percent of each ingredient.

Ln Cum% = 4.04 + 0.0132 x1 + 0.0518 x2 – 0.1994 x3 : r^2= 0.75 (equation 8)
where Cum% indicates the cumulative percent of drug extracted over the entire time interval, and x1, x2 and x3 are the weight percents of EL, IPM and CAB 381-20.
As can be seen, the weight percent of drug that was extracted by the above described alcoholic solution decreased with increasing CAB 381-20 (see formulations 256-62-02, 256-62-04, 256-62-06 and 256-62-08). However, it was not obvious that the addition of well known rheology modifier, IPM, when added to the formulations containing 4 wt. % of CAB 381-20, did not affect the alcohol extraction of the drug as demonstrated by Formulation 256-62-16. This is contrary to a common sense in the art of pharmaceutical formulations. That is IPM , which is a rheology modifier of SAIB, would have been predicted to loosened up the SAIB formulations and facilitated the drug extraction but it did not. It was also discovered that when the CAB content was 3 wt. % as in formulation 256-62-12, addition of 3 wt. % of IPM increased significantly the drug extractability by alcohol solution versus the formulations that did not contain IPM such as formulation 256-62-04. It was concluded therefore, that low drug extractability from SAIB formulations by alcohol can be brought about not only due to optimum weight percent of CAB but also due to an optimum ratio between CAB and IPM.

FIG. 2 shows cumulative percent of oxycodone free base extracted by alcohol vs. time (mins) for 4 formulations. Each formulation was filled into soft gelcaps. Each gelcap contained 12 mg/ml oxycodone free base.

In this experiment the effects of different ratios of IPM to CAB were evaluated for drug extractability from SAIB formulations by alcohol. The ratio varied from 0.25 to 0.78. For the given range of ratios, it was discovered unexpectedly that increasing contents of ethyl lactate, isopropyl myristate and CAB in concert reduced the drug extractability by alcoholic solution. From this experiment, it was discovered that IPM and CAB were quantitatively reciprocally interchangeable, such that increasing one component and decreasing the other by the same wt% resulted in a formulation with unchanging rheological properties. This is particularly surprising discovery in light of the fact that IPM is a rheology modifier that makes the SAIB formulation loose (less viscous) while CAB is supposed to make it more cohesive and less deformable. One would not have expected, therefore, that increasing IPM would have the same effect as increasing CAB.

FIG. 3 shows cumulative percentage of drug extracted by alcoholic solution from various SAIB formulations vs. time (mins) for 4 formulations. Each formulation contains 12 mg/ml oxycodone. These formulations had IPM to CAB ratios ranging from 0.6 to 0.78 and calibrated content of ethyl lactate ranging from 27 –29 wt. %. The figure demonstrates that at the end of 180 minute extraction experiment, the percentage extracted was approximately the same for all 4 formulations. However, at the end of the first 60 minutes, it was discovered that the percent extracted drug was higher with the formulations containing greater amounts of ethyl lactate. It was also found that extremely an small increment in ethyl lactate content led to a large increase in the extraction of drug.

FIG. 4 Shows cumulative percentage of drug extracted by alcohol vs. time (mins) for 3 formulations. Each formulation contains 9 mg/ml oxycodone. This experiment demonstrated that ethyl lactate has greater influence on the drug extractability by alcohol than CAB by a factor of more than 2 fold. This was another unexpected discovery since it would have been reasonable to believe that CAB is a extremely effective matrix/network forming agent.

FIG. 11 shows the results of alcohol-extraction experiments. The graph displays a plots of % total oxycodone extracted into 40% ethanol + 0.1N HCl vs. time. The control formulation used was a commercial 10mg Oxycontin® tablet. The experimental formulations used in this experiment did not contain IPM and had the following ratios of SAIB:EL:CAB: "Base Formula, high level" = 50:45:5; "Base Formula, medium level" = 60.8:37:2.2; "Base Formula, low level" = 50:48:2. In this experiment, at about 30 minutes, the gelatin capsule containing formulations disclosed herein was cut in half, and the tablet was crushed with a spatula. As can be seen, the OxyContin® tablet formulation rapidly releases 100% of drug after crushing. After about 60 minutes, all the drug is released. For the three SAIB formulations, however, the % drug released after 60 mins is only about 13%, 23% and 30% for the low, medium and high formulations, respectively. These results clearly demonstrate that the formulations of the invention have significantly improved abuse-deterrence characteristics when compared with the current Oxycontin® tablet formulation.

Extraction of Drug Into Water

Another experiment was performed to determine the degree to which the formulation of the invention possessed abuse deterrent characteristics, specifically to determine the extractability of Oxycodone into water. Typically, a drug abuser may crush and grind an oxycodone tablet and dissolve it in water to extract the drug into aqueous solution for injecting. In the present experiment, the experimental dosage form was a SAIB-oxycodone gelcap with a formulation of SAIB:EL:IPM:CAB at a ratio of 67:26:3:4, contained in a soft gelatin capsule, and containing 9mg of drug (oxycodone free base). The control dosage form used was a 9mg Oxycontin® tablet. Each dosage form was crushed with a mortar and pestle and ground in 5ml water. The resulting solution/suspension was then filtered through a 0.45 micron filter into a flask and diluted to 50 ml with water. Oxycodone concentration was then quantified by HPLC. The results were as follows: For the control (OxyContin® tablets), 100% of the oxycodone was extracted from the crushed tablet into water. For the experimental SAIB formulation, only about 21% of oxycodone extracted into water. This shows that the current formulation has considerable drug-abuse deterrence characteristics when

compared with the Oxycontin® tablet, because the drug cannot be efficiently extracted into water.

Physical Treatment

Another potential method for drug abuse is to lower the temperature and mechanically crush a drug formulation so as to produce a powder which then can be inhaled or dissolved in a solution for injection. An experiment was performed to determine the characteristics of the current formulation, specifically with regard to lowering the temperature and crushing. In this procedure the formulation was placed in a laboratory freezer at –80 °Cfor eight hours, after which it was struck sharply with a hammer. One formulation comprised 100% SAIB, one formulation comprised SAIB plus a solvent (26%EL), and one formulation was a formulation of SAIB:EL:IPM:CAB at a ratio of 67:26:3:4 and oxycodone free base(see above). For the first formulation (100% SAIB) the results were as follows: Within about 45 seconds of being crushed, the fragments thawed and returned to the state of a high viscosity liquid. The controlled release matrix structure of the formulation was preserved. For the second formulation (SAIB + solvent): Within about 30 seconds after being crushed the formulation mass appeared highly viscous and sticky and did not fracture into discreet fragments. Again, the controlled release matrix structure was preserved. For the PTI-821 formulation: Within about 30 seconds after being crushed the formulation appeared highly viscous and tacky and did not fracture into fragments. Once again, the controlled release matrix structure was preserved. Consequently, attempted abuse by lowering temperature and crushing would not result in a readily abusable form of drug. See figures 8-10.

Plasma Level Study

FIG. 5 is a graph from a dog PK study showing plasma concentration (ng/ml) vs. time (hr) for three SAIB soft gelcaps containing 9 mg oxycodone formulations (A, B and C) and Oxycontin® (A=SAIB:EL:CAB; B=SAIB:EL:CAB; C=SAIB:EL:CAB, CAB=CAB 171-15). A single gelcap containing about 0.75g of each of oxycodone formulations was administered to a dog orally. Blood was drawn periodically over 12 hours and the plasma concentration of oxycodone was determined as a function of time.

Plasma vs. time profiles for three formulations A, B and C, were compared against that for Oxycontin®. The SAIB gelcap formulations and the Oxycontin® tablets each contained an identical amount of oxycodone free base (9 mg).

SAIB formulations A and C exhibited higher Cmax (maximum plasma concentration of drug) values than the Oxycontin® tablet formulation. The two SAIB formulations A and B had a significantly shorter Tmax (time to maximum plasma level) values compared with Oxycontin®. On the other hand, SAIB formulation B which has a highest viscosity of A, B and C, shows equivalent Cmax but longer Tmax values compared with the Oxycontin® control.

SAIB formulations A and C also gave greater AUC (area under the plasma drug concentration vs. time curve) values and bioavailability due to their unique rheological (flow) characteristics compared to Oxycontin® reference. It was discovered that optimum SAIB formulations, which manifest desirable pharmacokinetic profiles, must possess the following viscosity characteristics: the SAIB solution viscosity at 37 °C should be in the range from 1,000 –30,000 cP. Further more the SAIB formulations following immersion in 37 °C water or aqueous buffer (pH 1-10) for 4-5 hours should optimally have the viscosity at 37 °C ranging from 3,000-50,000 cP.

Although a number of the examples provided above relate to compositions according to the invention containing oxycodone in amounts of approximately 10 mg per SAIB formulation gelcap, larger or smaller amounts of drug (e.g., 5 mg, 20 mg, 40 mg, 80mg, 160 mg, and the like) can be incorporated into SAIB gelcaps according to the invention.

While the benefits of the invention have been described with respect to certain drugs, such as opioids, some or all of these benefits are obtained when the formulation of the invention is used with a wide variety of drugs, such as immunosuppressants, antioxidants, anesthetics, chemotherapeutic agents, steroids (including retinoids), hormones, antibiotics, antivirals, antifungals, antiproliferatives, antihistamines, anticoagulants,

antiphotoaging agents, melanotropic peptides, nonsteroidal and steroidal anti-inflammatory compounds, antipsychotics, and radiation absorbers, including UV-absorbers,chemotherapeutic agents, anti-nausea medication, and the like. Non-limiting examples of pharmacological materials or drugs suitable for use in the invention include anti-infectives such as nitrofurazone, sodium propionate, antibiotics, including penicillin, tetracycline, oxytetracycline, chlorotetracycline, bacitracin, nystatin, streptomycin, neomycin, polymyxin, gramicidin, chloramphenicol, erythromycin, and azithromycin; sulfonamides, including sulfacetamide, sulfamethizole, sulfamethazine, sulfadiazine, sulfamerazine, and sulfisoxazole, and anti-virals including idoxuridine; antiallergenics such as antazoline, methapyritene, chlorpheniramine, pyrilamine prophenpyridamine, hydrocortisone, cortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone, triamcinolone, medrysone, prednisolone, prednisolone 21-sodium succinate, and prednisolone acetate; desensitizing agents such as ragweed pollen antigens, hay fever pollen antigens, dust antigen and milk antigen; vaccines such as smallpox, yellow fever, distemper, hog cholera, chicken pox, antivenom, scarlet fever, dyptheria toxoid, tetanus toxoid, pigeon pox, whooping cough, influenzae rabies, mumps, measles, poliomyelitic, and Newcastle disease; decongestants such as phenylephrine, naphazoline, and tetrahydrazoline; miotics and anticholinesterases such as pilocarpine, esperine salicylate, carbachol, diisopropyl fluorophosphate, phospholine iodide, and demecarium bromide; parasympatholytics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine; sympathomimetics such as epinephrine; sedatives and hypnotics such as pentobarbital sodium, phenobarbital, secobarbital sodium, codeine, (a-bromoisovaleryl) urea, carbromal; psychic energizers such as 3-(2-aminopropyl) indole acetate and 3-(2-aminobutyl) indole acetate; tranquilizers such as reserpine, chlorpromayline, and thiopropazate; androgenic steroids such as methyl-testosterone and fluorymesterone; estrogens such as estrone, 17-.beta.-estradiol, ethinyl estradiol, and diethyl stilbestrol; progestational agents such as progesterone, megestrol, melengestrol, chlormadinone, ethisterone, norethynodrel, 19-norprogesterone, norethindrone, medroxyprogesterone and 17-.beta.-hydroxy-progesterone; humoral agents such as the prostaglandins, for example PGE_1, PGE_2 and PGF_2 ; antipyretics such as aspirin, sodium salicylate, and salicylamide;

antispasmodics such as atropine, methantheline, papaverine, and methscopolamine bromide; antimalarials such as the 4-aminoquinolines, 8-aminoquinolines, chloroquine, and pyrimethamine, antihistamines such as diphenhydramine, dimenhydrinate, tripelennamine, perphenazine, and chlorphenazine; cardioactive agents such as dibenzhydroflume thiazide, flumethiazide, chlorothiazide, and aminotrate; nutritional agents such as vitamins, natural and synthetic bioactive peptides and proteins, including growth factors, cell adhesion factors, cytokines, and biological response modifiers.

The embodiments disclosed herein are exemplary only, and are not meant to limit the invention, which should be interpreted solely in light of the claims.